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(54) Title: PHARMACEUTICAL FORMULATIONS FOR AEROSOLS WITH TWO OR MORE ACTIVE SUBSTANCES

(57) Abstract

The present invention relates to new pharmaceutical formulations for aerosols with at least two or more active substances for administration by inhalation or by nasal route. Specifically, the invention relates to pharmaceutical preparations for propellant-driven metered dose aerosols using a fluorohydrocarbon (HFC) as propellant, which contain a combination of active substance of two or more active substances, wherein at least one active substance is present in dissolved form together with at least one other active substance in the form of suspended particles.

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Prosecution application

Pharmaceutical Formulations for Aerosols with two or more Active Substances

The present invention relates to new pharmaceutical formulations for aerosols with at least two or more active substances for use by inhalation or by the nasal route.

State of the art

In propellant-driven metered dose inhalers (MDI) the active substances can be formulated as solutions or suspensions. The vast majority of aerosol formulations for MDI's are prepared as suspensions, especially if the preparation contains more than one active substance. Formulations in the form of solutions are used only to a limited extent. In these cases, the formulations normally contain only one active substance.

As a rule, in a suspension, the chemical stability of the active substances is noticeably higher than in a solution. Additionally, in a suspension the active substance can be more highly concentrated than in a solution, with the result that suspension type formulation enable higher doses to be administered.

A major disadvantage of suspension-formulations is the fact that over time (e.g. during storage) the suspended particles clump together to form bigger, more or less stable agglomerates or form loose flakes, sediments or floating layers, or in the worst case, particle growth, which significantly impairs the pharmaceutical quality of the product. The size of the particles formed or the

speed of particle growth are influenced by the solubility features of the liquid phase. Thus, ingress of humidity during storage or a desired increase in polarity, e.g. achieved by adding co-solvents, can have a devastating effect on the quality of the medical end product, particularly if the suspended particles have polar structure elements. The suspension can be physically stabilised by the addition of surfactants, by reducing the harmful effects of moisture and/or particle growth so that suspended particles can be held in suspension for longer.

Natural solution-type formulations are not affected by the problems of increasing particle size or de-mixing processes such as sedimentation or flocculation. However, in this case there is a serious risk of chemical degradation. A further disadvantage is the fact that the limited solubility of the ingredients can prevent administration in high doses. In the past, the chlorofluorohydrocarbons TG 11 (trichlorofluoromethane), TG 12 (dichlorodifluoromethane) and TG 114 (dichlorotetrafluoroethane) have proved particularly suitable as solvents. The solubility of the ingredients can be increased by the addition of co-solvents. In addition, it is usually necessary to take additional measures to chemically stabilise the dissolved components.

Up till now, CFCs such as the above-mentioned TG 11, for example, have often been used as propellants. However, since CFCs have been linked with the destruction of the ozone layer, their manufacture and use are being phased out. The intention is to replace them with special fluorohydrocarbons (HFC) which are less destructive to the ozone layer but have completely different solubility features. The toxicological profile and physico-chemical properties such as the steam pressure, for example, determine which HFCs are suitable for MDIs. The most

promising representatives at present are TG 134a (1,1,2,2-tetrafluoroethane) and TG 227 (1,1,1,2,3,3,3-heptafluoropropane).

For inhalative treatment it may be desirable to have aerosol formulations with two or more active substances. In such cases the active substances are formulated in the necessary concentrations as solutions or suspensions, frequently giving rise to problems regarding the chemical stability of the individual substances or the degree of concentration which can be attained. Major problems are encountered if one of the active substances cannot be suspended or is unstable in a suspension-type formulation of this kind or if one of the active substances is chemically unstable or will not dissolve in a solution-type formulation of this kind, particularly when HFC is used as the propellant.

It is therefore one object of the present invention to develop a formulation for metering aerosols having two or more active substances which overcomes the above-mentioned disadvantages.

Description of the invention

Surprisingly, it has been found that a plurality of active substances can be formulated as a solution and a suspension combined in one formulation.

The invention relates to stable aerosol formulations with fluorohydrocarbons as propellants, particularly TG 134a and/or TG 227, consisting of two or more active substances, wherein at least one active substance is formulated as a solution and at least one active substance is formulated as a suspension. The pharmaceutical preparation according to the invention is used for

inhalative treatment, particularly for treating diseases of the pharynx and respiratory tract, e.g. asthmatic diseases and COPD.

Detailed description of the invention

In one embodiment a medicinally useful combination of two or more active substances is used, containing beclometasone, budesonide, cromoglycinic acid, fenoterol, flunisolide, fluticasone, ipratropium bromide, nedocromil, orciprenaline, oxitropium bromide, reproterol, salbutamol (albuterol), salmeterol, terbutalin, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide, the esters, salts and/or solvates thereof. Which of the above-mentioned active substances is formulated as a solution and which as a suspension in the preparation according to the invention depends on the particular combinations of active substance and can be determined relatively quickly by solution and suspension trials.

In a preferred embodiment, one or more of the following active substances are suspended: budesonide, cromoglycinic acid, nedocromil, reproterol and/or salbutamol (albuterol) or the esters, salts and/or solvates derived from these compounds and one or more of the following substances are dissolved: beclomethasone, fenoterol, ipratropium bromide, orciprenaline and/or oxitropium bromide, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide or the esters, salts and/or solvates derived from these compounds. Embodiments having two different active substances are preferred.

A particularly preferred embodiment contains dissolved ipratropium bromide, particularly combined with salbutamol

sulphate (albuterol sulphate) as the suspended active substance.

In all the embodiments, the active substances are used in a therapeutically effective quantity, i.e. in a quantity that can induce a successful treatment. The concentration of the active substances and the volume per stroke of spray are adjusted in such a way that the quantity of active substance which is medically necessary or recommended is released by a single spray or by a few sprays.

One embodiment relates to formulations in which the suspended particles are stabilised by the addition of surfactant substances (surfactants) or other suspension-stabilising agents to stabilise the suspended particles against physical changes. The benefit of this is that the particle size will remain pharmaceutically acceptable even over lengthy periods, e.g. during storage. Preferred particle sizes are up to 20 µm, whilst particularly preferred particle sizes are between 5 and 15 µm, best of all not exceeding 10 µm. The advantage of these particle sizes is that the particles are small enough to penetrate deeply into the lungs but not so small as to be breathed out again with the exchanged air.

Suitable surfactants and suspension-stabilising agents include all pharmacologically acceptable substances which have a lipophilic hydrocarbon group and one or more functional hydrophilic groups, especially C_{5-20} fatty alcohols, C_{5-20} fatty acids, C_{5-20} fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethylenes, polysorbates, sorbitan esters and/or carbohydrates. C_{5-20} fatty acids, propyleneglycol diesters and/or triglycerides and/or sorbitans of the C_{5-20} fatty acids are preferred, whilst oleic acid and sorbitan mono-,

di- or trioleates are particularly preferred. Alternatively, toxicologically and pharmaceutically acceptable polymers and block-polymers can be used as suspension-stabilising agents. The surfactants used are either non-fluorinated or partially fluorinated or perfluorinated, the term fluorinated referring to the exchange of hydrogen radicals bound to the carbon for fluorine radicals. The quantity of surfactant may be up to 1:1 based on the proportion by weight of the suspended active substances; amounts of 0.0001:1 to 0.5:1 are preferred, whilst amounts of from 0.0001:1 to 0.25:1 are particularly preferred.

A further advantage of the above surfactants is that they can also be used as valve lubricants. Therefore, one embodiment relates to formulations in which said surfactants are added as valve lubricants.

In another embodiment the solubility of at least one active substance to be dissolved is increased by the addition of one or more co-solvents. This has the advantage that the active substance or substances to be dissolved can be formulated in higher concentrations. The addition of co-solvent must not exceed the critical threshold of polarity of the liquid phase at which one of the disadvantages described above begins to affect the suspended particles of active substance.

Suitable co-solvents are pharmacologically acceptable alcohols such as ethanol, esters or water or mixtures thereof; ethanol is preferred. The concentration of the co-solvent in relation to the total formulation may be from 0.0001 to 50 wt.-%, preferably 0.0001 to 25 wt.-%. In another embodiment a concentration of 0.0001 to 10 wt.-% is preferred whilst particularly preferred embodiments are those wherein just enough alcohol is added

to dissolve the active substance which has to be dissolved.

In another embodiment, other common propellants are added to the HFC propellant. These added propellants may be, beside other HFCs, saturated lower hydrocarbons such as propane, butane, isobutane or pentane provided that the mixture is pharmacologically acceptable.

In one embodiment, stabilisers are added to the formulation, with a beneficial effect on the pharmaceutical stability of the active substances even over lengthy periods, e.g. during storage. In the context of the invention, stabilisers denotes those substances which prolong the durability and usability of the pharmaceutical preparation by preventing or delaying chemical changes in the individual ingredients, particularly the active substances, e.g. caused by subsequent reactions or degradation, or those which prevent biological contamination. Stabilisers which are preferred for this purpose are those which influence the pH of the liquid phase, such as acids and/or the salts thereof, particularly suitable substances are hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid and the salts thereof. In addition, preferred bactericides, fungicides etc. are benzalkonium chloride or ethylene diamine tetraacetate. Citric acid is most preferred. The concentration of the stabilisers may be up to 1000 ppm, preferably up to 100 ppm and most preferably 20 to 40 ppm.

One particularly preferred embodiment comprises suspended salbutamol sulphate (albuterol sulphate), dissolved ipratropium bromide, ethanol as co-solvent and citric acid as stabiliser.

Examples

Example 1

In a solution of liquefied 89.96 g (1 mol, 89.71 wt.-%) of TG 134a and 10.03 g (218 mmol, 10.00% by weight) of ethanol are dissolved 37 mg (0.09 mmol, 0.037 wt.-%) of ipratropium bromide and 4 mg (20 µmol, 0.004% by weight) of citric acid and 210.5 mg (0.88 mmol, 0.21% by weight) of salbutamol sulphate (albuterol sulphate) are suspended together with 0.05% by weight of surfactant (e.g. 50 mg (177 mmol) of oleic acid).

Example 2

Analogous to Example 1 using TG 227 as the propellant gas instead of TG 134a.

Example 3

Disodium chromoglycate is suspended in liquefied P134 and a small amount of ethanol and fenoterol hydrobromide is dissolved therein.

Example 4

Analogous to Example 3 using TG 227 as propellant gas instead of TG 134a.

Patent Claims

1. Pharmaceutical preparation for propellant driven metered dose inhalers having a fluorohydrocarbon (HFC) as propellant, which contain a combination of two or more active substances characterised in that at least one active substance is present in dissolved form by the use of a co-solvent together with at least one other active substance in the form of suspended particles.

2. Pharmaceutical preparation according to claim 1, characterised in that the combination of active substances consists of two active substances.

3. Pharmaceutical preparation according to one of the preceding claims, characterised in that the propellant is TG 134a and/or TG 227.

4. Pharmaceutical preparation according claim 3, characterised in that the co-solvent comprises one or more pharmacologically tolerable alcohols, a pharmacologically tolerable ester, water or a mixture thereof.

5. Pharmaceutcal preparation according to claim 3, characterised in that the co-solvent is ethanol.

6. Pharmaceutical preparation according to claim 3, 4 or 5 characterised in that the co-solvent is present in a concentration of up to 25% by weight, based on the quantity of liquefied propellant.

7. Pharmaceutical preparation according to claim 3, 4, 5 or 6, characterised in that the co-solvent is present

in a concentration of up to 10% by weight, based on the quantity of liquefied propellant.

8. Pharmaceutical preparation according to claim 1, 2,3, 4, 5, 6 and 7, characterised in that the composition is stabilised by a stabiliser.

9. Pharmaceutical preparation according to claim 8, characterised in that the stabiliser contains one or more acids and/or salts.

10. Pharmaceutical preparation according to claim 8 or 9, characterised in that the stabiliser(s) contain(s) hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, ascorbic acid, citric acid, benzalkonium chloride and/or ethylene diamine tetraacetic and/or a salt thereof.

11. Pharmaceutical preparation according to claim 8 to 10, characterised in that the stabiliser is citric acid.

12. Pharmaceutical preparation according to one of the preceding claims 8 to 11, characterised in that the stabiliser is present in an amount of up to 100 ppm.

13. Pharmaceutical preparation according to one of the preceding claims 8 to 11, characterised in that the stabiliser is present in an amount of up to 40 ppm.

14. Pharmaceutical preparation according to one of the preceding claims 1 to 13, characterised in that the preparation contains a surfactant or suspension-stabilising agent.

15. Pharmaceutical preparation according to claim 14, characterised in that the surfactant contains C_{5-20} fatty alcohols, C_{5-20} fatty acids, C_{5-20} fatty acid esters, lecithin, glycerides, propyleneglycol esters, polyoxyethanes, polysorbates, sorbitan esters and/or carbohydrates.

16. Pharmaceutical preparation according to claim 14, characterised in that the surfactant contains C_{5-20} fatty acids and/or the esters thereof.

17. Pharmaceutical preparation according to claim 14, characterised in that the surfactant contains oleic acid and/or sorbitan mono-, di- or trioleate.

18. Pharmaceutical preparation according to claim 14, characterised in that the surfactant contains oleic acid.

19. Pharmaceutical composition according to claim 14 characterised in that the surfactant or suspension-stabilising agent comprises a toxicologically acceptable polymer and/or block-polymer.

20. Pharmaceutical preparation according to one of the preceding claims, characterised in that the active substance combination contains beclomethasone, budesonide, cromoglycinic acid, fenoterol, flunisolide, fluticasone, ipratropium, nedocromil, orciprenaline, oxitropium bromide, reproterol, salbutamol, salmeterol (albuterol), terbutalin, N-[[2,2-dimethyl-4-(2-oxo-2H-pyridin-1-yl)-6-trifluoromethyl-2H-1-benzopyran-3-yl]methyl]-N-hydroxy-acetamide, the esters, salts and/or solvates thereof.

21. Pharmaceutical preparation according to one of claims 1 to 20, characterised in that the active substance combination contains salbutamol sulphate (albuterol sulphate) and ipratropium bromide.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/12 A61K31/135 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01147 A (RHONE POULENC RORER LTD ;BELL ALEXANDER (GB)) 15 January 1998 (1998-01-15)	1-7,14
Y	page 2, line 22-25 page 3, line 1-23 page 4, line 17 -page 5, line 8 examples 3,4 claims 1-4,6,12,20	20,21
X	US 5 589 156 A (HENRY RICHARD A) 31 December 1996 (1996-12-31) abstract column 3, line 13-31 column 7, line 35-60 claims	1,3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 603 918 A (MCNAMARA DANIEL) 18 February 1997 (1997-02-18) column 2, line 31-59 examples claims	20,21
A	WO 94 13262 A (JAGER PAUL D ;KONTNY MARK J (US); NAGEL JURGEN H (DE)) 23 June 1994 (1994-06-23) page 4, line 12-21 page 5, line 22,23 page 6, line 1-7 page 8, line 3-6 page 10, line 6-11 page 10, line 17-30 page 16 -page 18; tables 2-4 claims 1-3,6,8-10,12,32	1,3-6, 8-18,20, 21
A	EP 0 499 344 A (RIKER LABORATORIES INC) 19 August 1992 (1992-08-19) page 2, line 39-50 page 4, line 36 -page 5, line 5 page 6, line 1-10 examples 4-6,24 claims 1,2,6,10,12	1,3-6, 14-21

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/US 99/12785

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9801147 A	15-01-1998	AU	3453897 A	02-02-1998
		EP	0914143 A	12-05-1999
US 5589156 A	31-12-1996	US	5534242 A	09-07-1996
		US	5453445 A	26-09-1995
		US	5593661 A	14-01-1997
		AU	4711396 A	08-10-1996
		CA	2215680 A	26-09-1996
		WO	9629066 A	26-09-1996
		EP	0814793 A	07-01-1998
		JP	11502202 T	23-02-1999
		US	5858331 A	12-01-1999
		AU	4711496 A	16-10-1996
		CA	2215711 A	03-10-1996
		WO	9630008 A	03-10-1996
		EP	0814794 A	07-01-1998
		JP	11502526 T	02-03-1996
		US	5679325 A	21-10-1997
US 5603918 A	18-02-1997	NONE		
WO 9413262 A	23-06-1994	AT	177941 T	15-04-1999
		AU	680227 B	24-07-1997
		AU	5740594 A	04-07-1994
		AU	6048694 A	04-07-1994
		BG	99760 A	29-02-1996
		CZ	9501490 A	13-12-1995
		DE	69324161 D	29-04-1999
		EP	0673240 A	27-09-1995
		ES	2129117 T	01-06-1999
		FI	952842 A	09-06-1995
		GB	2288978 A,B	08-11-1995
		HU	72985 A	28-06-1996
		JP	8509459 T	08-10-1996
		LV	10911 A	20-12-1995
		LV	10911 B	20-04-1996
		NO	952269 A	08-06-1995
		NZ	259192 A	26-05-1997
		PL	309333 A	02-10-1995
		SG	52459 A	28-09-1998
		SK	76095 A	08-01-1997
		WO	9413263 A	23-06-1994
		US	5676930 A	14-10-1997
		CN	1095265 A	23-11-1994
		ZA	9309195 A	08-06-1995
EP 0499344 A	19-08-1992	AU	631155 B	19-11-1992
		AU	4595689 A	14-06-1990
		CA	2004598 A	06-06-1990
		DE	68924540 D	16-11-1995
		DE	68924540 T	15-05-1996
		DK	595789 A	07-06-1990
		EP	0372777 A	13-06-1990
		EP	0653204 A	17-05-1995
		ES	2045470 T	16-01-1994
		ES	2077971 T	01-12-1995
		HK	7196 A	26-01-1996
		HK	80497 A	20-06-1997

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter nal Application No
PCT/US 99/12785

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0499344 A		IL 92457 A	21-10-1994
		JP 2200627 A	08-08-1990
		JP 2786493 B	13-08-1998
		MX 9203480 A,B	01-07-1992
		US 5695743 A	09-12-1997
		US 5683677 A	04-11-1997
		US 5674473 A	07-10-1997
		US 5225183 A	06-07-1993
		US 5766573 A	16-06-1998
		US 5776434 A	07-07-1998
		US 5720940 A	24-02-1998